Journal of Tissue Science & Engineering

ISSN: 2157-7552

Pucar et al., J Tissue Sci Eng 2017, 8:3

DOI: 10.4172/2157-7552.1000213

Review Article

Open Access

Wound Healing Process, Diabetes and Implications of Dipeptidyl Peptidase IV (DPP IV/CD26)

Lara Baticic Pucar[1]*, Anja Kovac[2], Dijana Detel[1], Suncica Buljevic[1], Ester Pernjak Pugel[3] and Jadranka Varljen[1]

[1]*Department of Chemistry and Biochemistry, Faculty of Medicine, University of Rijeka, Brace Branchetta 20, 51000 Rijeka, Hrvatska, Croatia*

[2]*Student at the Department of Biotechnology, University of Rijeka, Radmile Matejcic 2, 51000 Rijeka, Hrvatska, Croatia*

[3]*Department of Histology and Embryology, Faculty of Medicine, University of Rijeka, Brace Branchetta 20, 51000 Rijeka, Hrvatska, Croatia*

Abstract

Dipeptidyl Peptidase IV or molecule CD26 (DPP IV/CD26) is a multifunctional protein, identified as a therapeutic target for type 2 diabetes, due to its ability to degrade incretins, insulin secretagogues. Delayed wound healing is a significant complication in diabetic patients that represents a major socio-economic health problem. It has been proposed that DPP IV/CD26 inhibition accelerates healing of chronic diabetic ulcers in those patients, through the induction of a histological pattern consistent with enhanced angiogenesis. Studies on mice models of diabetes-disturbed wound healing also suggested that the inhibition of DPP IV enzymatic activity may improve tissue regeneration processes. However, further research is needed to elucidate the role of DPP IV/CD26 in diabetic wound healing. The objective of this work was to discuss recent findings on the implications of DPP IV/CD26 in tissue regeneration and reparation in diabetic environment.

Keywords: Dipeptidyl peptidase IV; Molecule CD26; Diabetes; Wound healing

Introduction

Diabetes Mellitus (DM) is a life-long condition characterized by the presence of chronic hyperglycemia with impairment in the metabolism of carbohydrates, lipids and proteins. It is a multifactorial disease that occurs because of various pathophysiological causes and processes. DM is a major public health problem since globally, according to the latest report from the International Diabetes Federation; 415 million people were affected with DM in 2015, with increasing incidence and prevalence [1]. DM is mostly diagnosed in adults, but in the last 20 years, the incidence in the pediatric age group has markedly increased. Depending on different populations, variations between incidence rates are observed, unlike gender, where the incidence is equally distributed; it is more common in developed countries and the risk of occurrence increases with obesity, reduced physical activity and age [2,3].

DM represents a group of metabolic disorders that can be classified by etiology and pathology as type 1 or type 2 DM, gestational diabetes and "other specific types" (monogenic diabetes). Type 1 DM is a genetic disease characterized by autoimmune pancreatic beta cell destruction that leads to loss of insulin production, insulin deficiency and hyperglycemia. As the response to the loss of insulin secretion, abnormal function of alpha cells appears likewise excessive secretion of glucagon. In a healthy organism, glucagon secretion is suppressed by hyperglycemia, but in type 1 DM, an elevated glucagon concentration aggravates metabolic defects due to insulin deficiency. In response to insulin deficiency, uncontrolled lipolysis and elevated levels of free fatty acids occur in the plasma [4]. On the other hand, type 2 DM comprises a group of genetic diseases with similar symptoms and outcomes, but with different genetic backgrounds and pathophysiological processes. The dysfunction of beta cells leads to impaired insulin secretion, and as the main consequence, insulin resistance develops. Since insulin resistance occurs, beta cells increase the production of insulin in order to maintain blood glucose level and ensure normal body function. Over years, beta cells begin to fail, insulin secretion decreases, and blood glucose levels increase. Another defect found in type 2 DM is insulin deficiency due to beta cell exhaustion or genetic factors. Individuals with type 2 diabetes mostly exhibit intra-abdominal obesity, related to insulin resistance and deficiency, hypertension and dyslipidemia [2,5].

Complications of Diabetes

The development of diabetic complications could be classified according to different mechanisms of their pathophysiology into macrovascular, microvascular and neurologic complications. The most common cause of death related to the macrovascular complication is atherosclerosis of the coronary arteries. Pathophysiology of small and large vessel disease include effects on capillaries all over the body and effects on mostly involved organs, eyes and kidneys. Adult blindness and diabetic nephropathy are the most common consequences of diabetic retinopathy. The permeability of vascular and nerve tissues and the ability for their glucose intake into cells, without the presence of insulin, increases the glucose level in the cells. Disposal mechanisms consequently can cause damage to blood vessels and nerves. All mentioned complications lead to delayed wound healing in diabetes, emerged from impaired processes of complex mechanisms of tissue reparation and regeneration [6]. Diabetic neuropathy, described as a loss of sensation in feet, leads to the formation of foot ulcers, which is currently considered as the leading cause of hospital admissions of diabetic patients. Approximately 15% of diabetic patients are affected by a diabetic foot ulcer. It is a major health problem since it causes pain, suffering and poor life quality [7].

Therapeutic Approaches in Diabetes

Early diagnosis and treatment of DM are crucial in the prevention of its possible complications. Different diagnostic tests such as Random plasma test, Fasting plasma glucose test, Oral glucose tolerance test, and

***Corresponding author:** Lara Baticic Pucar, Department of Chemistry and Biochemistry, Faculty of Medicine, University of Rijeka, Brace Branchetta 20, Hrvatska, Croatia; Tel: 0038551651159; Fax: 0038551678895; E-mail: lara.baticic@medri.uniri.hr

Received December 06, 2017; **Accepted** December 12, 2017; **Published** December 17, 2017

Citation: Pucar LB, Kovac A, Detel D, Buljevic S, Pugel EP, et al. (2017) Wound Healing Process, Diabetes and Implications of Dipeptidyl Peptidase IV (DPP IV/CD26). J Tissue Sci Eng 8: 213. doi: 10.4172/2157-7552.1000213

others for identification of both types of diabetes are available, but the rate of undiagnosed patients is still high. Achieving balanced diabetes treatment is the key management strategy for treating patients with both type 1 and 2 DM. The first goal of the diabetic treatment is to achieve and maintain stable euglycemia and the process starts with a diabetic plan of nutrition as well as the administration of oral anti-hyperglycemic agents. Personalized insulin therapies in type 1 DM patients last for life. In type 2 DM, in response to insulin insufficiency, insulin therapy is also needed. Surgical management of diabetes is also available. In type 2 DM, circulating levels of glucose and fatty acids contribute to dysfunction of beta cells. To restore the deficient beta cells, transplantation of pancreatic islets cells, endowed with the capillary network is also a therapeutic option [2]. The success of the method is contributed by vascularization factors, one of them being vascular endothelial growth factor (VEGF), crucial for creating *de novo* blood vessels. Another important molecule for which it has been proven *in vivo* that expands islet mass by increasing beta cell number and induces islet neogenesis is glucagon-like-peptide 1 (GLP-1). However, its biological availability is controlled by dipeptidyl peptidase IV (DPP IV/CD26), a moonlighting protein with an enzymatic function which cleaves active GLP-1. One of the most important implications of DPP IV/CD26 inhibitors is indeed therapeutic support of DM, where it found its clinical importance, given its capability to contribute to the maintenance of glucose homeostasis [8].

Dipeptidyl Peptidase IV/Molecule CD26 (DPP IV/CD26)

Dipeptidyl peptidase IV (DPP IV/CD26, EC 3.4.14.5), the main member of the DPP IV/CD26 family of proteins, is a ubiquitous multifunctional transmembrane glycoprotein, present also in a soluble form in plasma and other biological fluids, acting as a proteolytic and costimulation molecule, and binding protein. It is known that DPP IV/CD26 cleaves off an N-terminal dipeptide from substrates with Ala or Pro in their penultimate position, but it is also known as the marker of cell surface T lymphocytes-CD26 and adenosine deaminase. It is expressed on the surface of various cell types in almost all tissues, including epithelial, endothelial and immune cells [9]. It plays a significant role in many physiological as well as pathological processes. DPP IV/CD26 was largely investigated since it is involved in the process of maintaining glucose homeostasis. Moreover, given the positive effects of DPP IV/CD26 inhibition in the mechanisms of chronic diabetic foot ulcers healing, as well as other pathologies, growing efforts are being made in order to elucidate the role of this molecule in crucial molecular pathways. It was shown that DPP IV/CD26 is implicated in key processes in wound healing. Its role in the regulation of cell adhesion, migration, apoptosis, angiogenesis and extracellular matrix degradation was previously confirmed. It was indicated that DPP IV/CD26 plays a particularly relevant role in tissue regeneration where it was found to influence inflammatory processes and impacts the process of epithelialization of wounds [6,7,10].

Molecular and Biological Properties of DPP IV/CD26

The relative molecular mass of a human DPP IV/CD26 dimer molecule is about 240 000 Da and contains 766 polypeptide residues. The transmembrane hydrophobic domain contains 22 amino acids, while the N-terminus contains a short intracellular sequence of 6 amino acids and a C-terminal catalytic region. The remaining 738 residues are located extracellularly and serve as glycosylation sites. The gene coding the DPP IV/CD26 protein is located on the long arm of chromosome 2q24.2 and contains 26 exons [11].

DPP IV/CD26 plays important roles in multiple biological fields ranging from immunology, glucose homeostasis, cancer biology, inflammation and various chronic diseases. At least five functions of DPP IV/CD26 have been shown so far: it has an enzymatic function as a serine protease, it acts as a receptor, an adhesion molecule for fibronectin and collagen and, as a protein, it is involved in ligand-receptor interactions. In the immune system, DPP IV/CD26 serves as a costimulatory surface molecule, modulating chemotaxis and influencing T-cell activity [12].

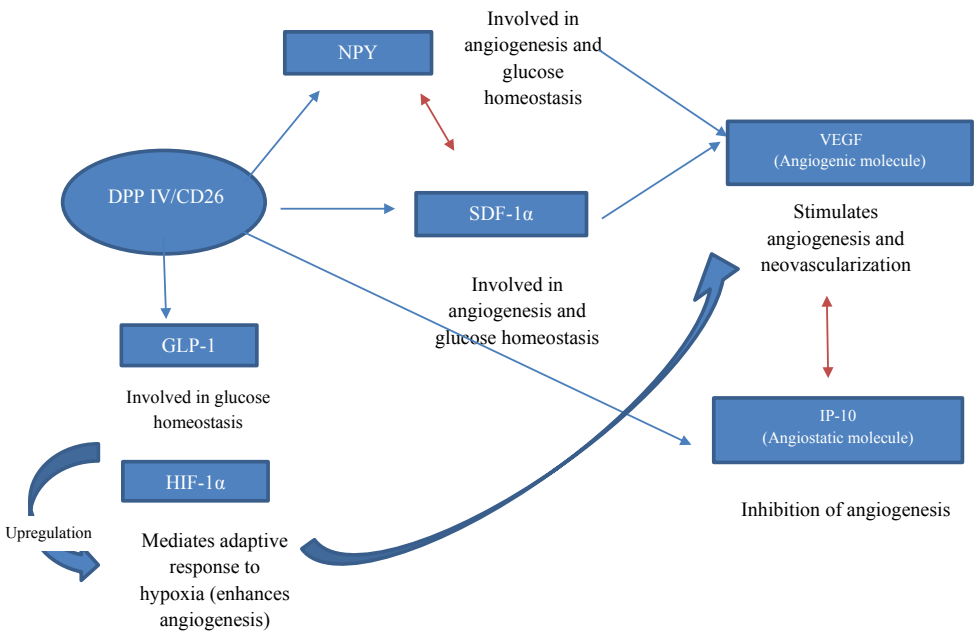

Figure 1: Schematic representation of causal connections between DPP IV/CD26 and its substrates, main molecules involved in angiogenesis and glucose homeostasis.

The presence of the amino acid proline gives unique structural features to peptides and many biologically important peptides, such as neuropeptides, hormones, cytokines, chemokines. Indeed, proline serves as a regulatory element in the process of proteolysis. DPP IV/CD26 is one of the members of a small group of proteases that recognize and cleave substrates that contain proline (or alanine) on the penultimate position in a polypeptide chain. The substrate specificity is arranged by the molecular environment of the active site [12,13].

Acting as a receptor, DPP IV/CD26 binds to adenosine deaminase (ADA). Because of ADA`s role in the development and function of lymphoid tissues, ADA deficiency causes defects in immune response and hematologic malignancies. The complex of ADA-DPP IV/CD26 reduces local concentrations of adenosine, while on the surface of T cells induces cell proliferation. After the catalytic action of DPP IV/CD26 on chemokines, it reduces their chemotactic activity. For instance, the colocalization of DPP IV/CD26 with the chemotactic receptor CXCR4, which is a receptor for stromal cell-derived factor 1α (SDF-1α), influences CXCR4-signaling properties for attracting endothelial progenitor cells at the inflammatory site. SDF-1α locally produced in damaged and inflamed tissues promotes angiogenesis and has an important role in diabetes as a protector of stem-cell-derived insulin-producing cells from glucotoxicity and as a promotor of beta-cell survival in mice [14].

Patients with type 2 DM show decreased insulin secretion and decreased effect of incretin hormones actions. The insulinotropic hormone GLP-1 is a DPP IV/CD26 substrate that shows a causal connection with wound healing in diabetic patients. DPP IV/CD26 cleaves the active form of GLP-1 (7-36) to form an inactive form of GLP-1 (9-36) thus modifying its biological activity [15]. After the processing of GLP-1 by DPP IV/CD26 enzymatic activity, its affinity for GLP-1 receptor decreases and effects directly on the production and activity of insulin (Figure 1). Active GLP-1 is important as it stimulates the excretion of glucose-stimulated insulin, increases the biosynthesis of insulin, stimulates the growth and proliferation of beta cells, and inhibits the excretion of glucagon [2]. An important role of DPP IV/CD26 inhibitors on decreasing proteasome activity was found in order to preserve angiogenic factors and angiogenesis at the wound site [7].

Biologically Important Molecules Related to DPP IV/CD26

NPY is a 36-amino acid neuropeptide, involved in the control of feeding, blood pressure, and energy homeostasis. It is known that NPY binds to 5 types of receptors (subtypes Y1-Y5). The receptor with significant properties in the processes of wound healing is the Y1 receptor, located on vascular smooth muscle cells, which promotes vasoconstriction and proliferation of cells. DPP IV/CD26 changes the ability of NPY to bind to its Y1 subtype of receptor and therefore terminates the action of NPY at the Y1 receptor, moderating thus the regulation of vascular smooth muscle contraction and angiogenesis [16]. Furthermore, an important role of NPY was noticed in pancreatic beta-cell survival as well as in glucose homeostasis, where NPY has the ability to suppress insulin secretion [14].

Substance P is a neuropeptide with important immunoregulatory functions that also acts as a potent contractor of smooth muscles. The cleavage of substance P by DPP IV/CD26 terminates its function in the degranulation of mast cells. A truncated substance P can further be cleaved by aminopeptidases, taking part in the degradation pathway in the vascular endothelium. Cleaved substance P directly inhibits insulin-dependent glucose metabolism in rats. Its involvement in diabetic corneal wound healing has also been shown [17]. Furthermore, it is known that DPP IV/CD26-mediated truncation of substance P could modulate the sense of pain in wounds [17,18] (Table 1).

Among molecules causally connected with DPP IV/CD26, a crucial role is played by VEGF, a factor that stimulates angiogenesis and neovascularization, the formation of granulation tissue and epidermal repair, having, therefore, a major role in wound healing. In diabetic patients, chronic non-healing wounds are often present. Low levels of active VEGF protein were found in diabetic wounds, which consequently leads to insufficient wound vascularization and delay in the tissue repair process [19].

Hypoxia-inducible factor 1α (HIF-1α) is a transcriptional factor responsible for gene transcription, whose protein products mediate adaptive responses to hypoxia. Under hypoxic conditions, HIF-1α promotes the upregulation of genes responsible for adaption in reduced oxygen environment [20]. Hypoxia encourages the release of growth factor VEGF, stimulating proliferation and migration of cells. HIF-1α regulates the expression of VEGF in the process of wound healing. It was shown that the active form of GLP-1 promotes the upregulation of HIF-1α. GLP-1 binds to its receptor (GLP-1R) situated mainly on pancreatic alpha and beta cells and therefore stimulates glucose-dependent insulin production. Previous studies evidenced that GLP-1 improves the generation of the angiogenic factor VEGF in human pancreatic islet environment [21]. Likewise, increased GLP-1 concentrations reduce the activation of the proteasome activity induced by oxidative stress [7]. In hyperglycemic conditions, HIF-1α is destabilized and its function is impaired, leading to delayed wound healing.

Another important substrate of DPP IV/CD26 involved in wound healing is the chemokine interferon-inducible protein 10 (IP-10 or CXCL10), which appears in homeostasis/coagulation phase, and plays a major role in the recruitment of activated CD4, CD8 and NK cells. Induced by infection and inflammation, the upregulation of the angiostatic molecule IP-10 causes vessel regression in the modeling phase of wound healing. In chronic wounds, the levels of inflammatory cytokines as well as IP-10 are increased. IP-10 is highly expressed during the granulation phase, but in chronic wounds, such as skin wounds in patients with type 2 diabetes, wounds remain static in the inflammatory phase and cannot proceed to the granulation stage [22].

Physiological System/Process	Regulatory Peptide/Chemokine/Hormone
Digestive and Vascular	Gastrin releasing peptide (GRP), glucagon-like peptide (GLP)-2, trypsinogen, pro-colipase, eneterostatin, aprotinin, bradykinin
Glucose metabolism and homeostasis	GLP-1 (7-37), glucagon, gastric inhibitory polypeptide GIP (1-42)
Endocrine and nervous	Pituitary adenylyl cyclase-activating peptide-1 (PACAP-1), vasostatin-1, thyrotropin-α, substance P (SP), neuropeptide Y (NPY), peptide YY (PYY), endomorphins
Immune	IL-2, IL-1β, RANTES, SDF-1α, SDF-1β, macrophage-derived chemokine (MDC), macrophage inflammatory protein (MIP)-1α and 1β, eotaxin, interferon-γ-inducible protein-10 (IP-10), interferon-inducible T-cell alpha chemoattractan (I-TAC), monocyte chemotactic protein (MCP)-1, -2 and -3, granulocyte chemotactic protein-2
Growth and healing	Insulin-like growth factor 1 (IGF-1), growth hormone releasing factor and hormone (GRFH and GRFR)

Table 1: Identified substrates of DPP IV/CD26 that directly or indirectly regulate various physiological functions [11-13,18].

DPP IV/CD26 mediates cleaving of IP-10, producing an antagonist form of the chemokine thus causing failure of vessel regression and tendency to ulceration and dehiscence. DPP IV/CD26 reduces the chemotactic ability of IP-10 and leaves the ability of IP-10 to inhibit angiogenesis [23].

DPP IV/CD26 Inhibitors in Treatment of Diabetes

DPP IV/CD26 inhibitors are oral hypoglycemic agents used either as a monotherapy of type 2 diabetes or in combination with other therapeutic agents such as metformin. The first clinical proof-of-concept study about the role of DPP IV/CD26 inhibitors in glucose-lowering treatment for type 2 diabetes was reported in the early 2000s [24]. It was first shown that the inhibition of DPP IV/CD26 elevates levels of circulating GLP-1, decreases glucagon concentrations and consequently lowers blood glucose levels. The research was based on known data about GLP-1 peptide as a potent anti-diabetic hormone. Findings of effects that DPP IV/CD26 inhibitors exert in preventing cleavage of GLP-1, hence increasing active GLP-1 in the circulation, led to further studies in the area of DPP IV/CD26 inhibitors development [25,26]. Today, numerous DPP IV/CD26 inhibitors are available and used in clinical practice, most common of them enlisted in Table 2.

Scientific research in the field of DPP IV/CD26 inhibitors has shown that administration of sitagliptin in diabetic mice decreases blood glucose levels and increases the number of beta cells in pancreatic islets of mice and pigs. Due to the increased number of beta cells, the insulin concentration increased in pancreatic islets [27]. Likewise, sitagliptin showed increased proliferation of endothelial cells around and inside of the grafts. The localization of cells that form microvessels within and around grafts, as well as localization of randomly distributed glucagon-positive cells around beta cells was found. Those findings suggested increased vascularization as a result of the activation of VEGF-A/VEGF-B signal pathway triggered by sitagliptin. Likewise, DPP IV/CD26 inhibition improved functional blood flow in grafts as a result of inhibitor acting. It is shown that sitagliptin improves VEGF secretion in transplanted porcine islets, which contributes to cell proliferation and angiogenesis by increasing VEGFR-2 expression [28]. DPP IV/CD26 inhibition with linagliptin also showed decreased blood glucose levels and accelerated skin re-epithelization in diabetic mice since levels of active GLP-1 in wound lysates increased. A reduced number of neutrophils and macrophages in linagliptin-treated mice were noted [29]. DPP IV/CD26 inhibitors also show pleiotropic effects by directly changing cytokine and growth factors expression, increasing plasma levels of SDF-1α and numbers of endothelial progenitor cells in circulation, which contributes to wound healing [30]. In clinical studies,

Brand Name	Active Ingredient(s)
Januvia	Sitagliptin
Janumet	Sitagliptin and Metformin
Janumet XR	Sitagliptin and Metformin extended release
Onglyza	Saxagliptin
Kombiglyze XR	Saxagliptin and Metformin extended release
Tradjenta	Linagliptin
Glyxambi	Linagliptin and Empagliflozin
Jentadueto	Linagliptin and Metformin
Nesina	Alogliptin
Kazano	Alogliptin and Metformin
Oseni	Alogliptin and Pioglitazone

Table 2: List of FDA-approved DPP IV/CD26 inhibitors in 2015 (FDA Drug Safety Communication available online at https://www.fda.gov/downloads/Drugs/DrugSafety/UCM460038.pdf).

DPP IV/CD26 inhibitor vildagliptin showed accelerated healing of chronic diabetic ulcers, with significantly faster rate of wound closure compared to the control group, most probably as a result of an increase in VEGF and HIF-1α, an important transcriptor factor with crucial role in neovascularization [7].

Role of DPP IV/CD26 in Wound Healing in Diabetes

The process of wound healing is a dynamic and complex course of action with the aim of regenerating damaged cellular structures and tissue layers that involves numerous cells such as endothelial cells, fibrocytes, kerationcytes and inflammatory cells. Wound healing is divided into several predictable phases: blood clotting (hemostasis), inflammation, tissue growth (proliferation), and tissue remodeling (maturation). Coagulation occurs one hour after the injury and is characterized by vasoconstriction and clot formation. Platelets come to the site of damaged blood vessels, initiate the clot formation and excrete various cytokines that attract inflammatory cells, growth factors and anti-inflammatory factors [31]. Growth factors in the inflammatory phase initiate angiogenesis and granulation by excreting growth factors such as TGF-β, IGF-1, MIP-1, MCP-2, TNF-α that trigger cell movement into the wound and play an important role in extracellular matrix formation. Growth factors VEGF and iNOS promote angiogenic activity [32]. The inflammatory phase follows the phase of proliferation characterized by tissue granulation and angiogenesis. Inflammatory cells such as neutrophils and macrophages help in wound debridement. Chemotactic factors attract monocytes to the wound where they differentiate into macrophages that remove bacteria and nonviable cells by phagocytosis. In the migration-proliferation phase, angiogenesis, contraction, and proliferation of keratinocytes occur. Fibroblasts proliferate inside the wound and make up the extracellular matrix, after which matrix metalloproteinases degrade synthesized collagen and form a scar. After collagen synthesis, the injured skin returns to its normal state. Due to angiogenesis, the supply of oxygen and nutrients again contribute to tissue functionality [33].

In diabetes, the process of wound healing is impaired due to numerous external and internal factors [34]. Chronic wounds, such as diabetic ulcers, show pathophysiological abnormalities that lead to impaired healing where the progression of tissue regeneration is not synchronized. Intrinsic factors such as neuropathy, vascular problems and other complications due to hyperglycemia cause impairment of wound healing in diabetic ulcers [35]. Extrinsic factors include repeated trauma or mechanical stress that lead to wound infection, the formation of callus and persistent ulcer formation. Exposure to high glucose concentration decreases proliferation and differentiation of keratinocytes. In diabetes, chemotaxis and phagocytosis are decreased in the early phase of wound healing, and the appearance of cytokine and growth factors in the wound is altered. Excessive deposition of collagens and fibronectin has also been reported in diabetic wounds [36,37].

Previous research has shown a significant role of DPP IV/CD26 in physiological and pathological processes. Important physiological functions of DPP IV/CD26 come with interactions with other proteins, such as ADA, substance P, VEGF, IP-10, glucagon and NPY [38]. DPP IV/CD26 plays an important role in wound healing at several levels: via its involvement in degradation of extracellular matrix (ECM), in cell adhesion and migration, and angiogenesis. DPP IV/CD26 causes degradation of ECM by binding to adenosine deaminase which leads to an increase of plasmin levels and the degradation of collagen, fibronectin, and laminin by activation of matrix metalloproteases

[39]. Previous studies have shown that DPP IV/CD26 stimulates the proliferation of T lymphocytes as well as chemokine secretion which is important for migration of inflammatory cells during the inflammatory phase. Extended duration of the inflammatory phase, in process of wound healing, can lead to chronic wounds and permanent tissue damage [31].

In addition, by acting on its substrate SDF-1α, DPP IV/CD26 decreases its chemotactic activity and consequently, SDF-1α loses its lymphocyte and monocyte chemotacticity and signaling properties for attracting endothelial progenitor cells at the inflammatory site. Furthermore, the enzymatic activity of DPP IV/CD26 on SDF-1α decreases its angiogenic properties. Likewise, DPP IV/CD26 acts proteolytically on its substrate NPY and terminates the action of NPY at its Y1 receptor subtype. Y1 is a receptor important for wound healing since it promotes vasoconstriction and proliferation of cells. Cleavage of NPY leads to the modulation of the regulation of vascular smooth muscle contraction and angiogenesis [40]. Its proteolytic activity on chemokines also affects cell migration and cell apoptosis. GLP-1 is a DPP IV/CD26 substrate which, under hypoxic conditions, promotes upregulation of HIF-1α, a regulator of expression of VEGF. VEGF stimulates angiogenesis and neovascularization, influences closing of the wounds, formation of granulation tissue and epidermal repair. Low VEGF activity in diabetic patient's leads to insufficient wound vascularization and delay in the repair process [19]. On the other side, a DPP IV/CD26 substrate, the chemokine IP-10, appears in the first phase of wound healing, homeostasis/coagulation phase and plays a role in the recruitment of activated CD4, CD8 and NK cells in the liver. DPP IV/CD26 mediates cleaving of IP-10, producing an antagonist form of the chemokine thus causing failure of vessel regression and tendency to ulceration and dehiscence. DPP IV/CD26 reduces the chemotactic ability of IP-10 and leaves the ability of IP-10 to inhibit angiogenesis [41].

From the aforementioned role of DPP IV/CD26 in wound healing, we can assume that DPP IV/CD26 plays a significant role by regulating the biological activity of its substrates such as cytokines and chemokines, and by its co-stimulatory actions on immune cells. Previous research has proven that DPP IV/CD26 impacts wound healing, as CD26 deficient mice showed better wound closure and scab formations compared to wild-type mice. Inhibition of DPP IV/CD26 activity during skin regeneration improves the clearance of elevated blood glucose levels and reduces high DPP IV/CD26 activity in chronic wound tissue of diabetic mice [29]. Animal studies in diabetic mice revealed increased DPP IV/CD26 levels in the presence of enhanced wound inflammatory conditions [42]. Our research group also demonstrated an important role of DPP IV/CD26 in the process of wound healing [43]. We showed an increase in epithelium thickness, corium connective tissue, and extracellular matrix was demonstrated in CD26 deficient mice during wound healing. Furthermore, an important role of DPP IV/CD26 has been shown in neovascularization: CD26 deficient mice show a prompt response in neovascularization and a higher number of capillaries on the second day of wound healing compared to wild-type mice. The impact of DPP IV/CD26 is also visible in cell proliferation, where the number of proliferating cells is higher in all analyzed days in CD26 deficient mice comparing to wild-type mice. The influence of DPP IV/CD26 on VEGF expression is related to the capability of DPP IV/CD26 to cleave GLP-1 which under hypoxic conditions promotes the upregulation of HIF-1α, a regulator of expression of VEGF. It was shown that on all days post wounding, VEGF expression was higher in CD26 deficient mice, as well as HIF-1α expression, which was twice higher in CD26 deficient mice than in wild-type mice. An impact of DPP IV/CD26 on immune cells at the site of tissue regeneration has also been noticed during the wound healing process. Moreover, DPP IV/CD26 influences the concentration of IP-10, an angiostatic molecule substrate of DPP IV/CD26 whose values are significantly higher in CD26 deficient animals during wound healing. Clinical studies as well showed that DPP IV/CD26 inhibitors may contribute to the healing of wounds. Vildagliptin, a DPP IV/CD26 inhibitor used in clinical practice induced increased levels of GLP-1, nitrotyrosine, proteasome 20S activity, HIF-1α, VEGF and capillary density, as well as improved wound healing in chronic diabetic ulcers [7] which opens new possibilities to pharmaceutical treatment of wound healing in diabetic patients.

Conclusion

Understanding the events of tissue regeneration provides a framework for developing new therapeutic agents with a positive impact on wound healing processes in diabetic patients. The inhibition of DPP IV/CD26, in addition to its established glycaemic control, shows positive impacts in the local wound healing in diabetic ulcers. Given the importance of DPP IV/CD26 in the regulation of glucose homeostasis as well as in the processes of tissue regeneration and reparation, this field indeed needs further scientific efforts in order to elucidate potential sites of pharmaceutical action aiming to manage devastating consequences of chronic diabetic ulcers.

References

1. Zimmet P, George Alberti K, Magliano DJ, Bennett PH (2016) Diabetes mellitus statistics on prevalence and mortality: Facts and fallacies. Nat Rev Endocrinol 12: 616–622.
2. Baynes HW (2015) Classification, pathophysiology, diagnosis and management of diabetes mellitus. J Diabetes Metab 6: 541.
3. Guthrie RA, Guthrie DW (2004) Pathophysiology of diabetes mellitus. Crit Care Nurs Q 27: 113-125.
4. Copenhaver M, Hoffman RP (2017) Type 1 diabetes: where are we in 2017. Transl Pediatr 6: 359-364.
5. Aschner P (2017) Recent advances in understanding/managing type 2 diabetes mellitus, F1000Res. F1000 Faculty Rev-1922.
6. Saboo A, Rathnayake A, Vangaveti VN, Malabu UH (2016) Wound healing effects of dipeptidyl peptidase-4 inhibitors: An emerging concept in management of diabetic foot ulcer - A review. Diabetes Metab Syndr 10: 113-119.
7. Marfella R, Sasso FC, Rizzo MR, Paolisso P, Barbieri M, et al. (2012) Dipeptidyl peptidase 4 inhibition may facilitate healing of chronic foot ulcers in patients with type 2 diabetes. Exp Diabetes Res 2012: 892706.
8. Samikannu B, Chen C, Lingwal N, Padmasekar M, Engel FB, et al. (2013) Dipeptidyl Peptidase IV inhibition activates creb an improves islet vascularization through VEGF-A/VEGFR-2 signaling pathway. PLoS ONE 8: e82639.
9. Fuchs H, Binder R, Greischel A (2009) Tissue distribution of the novel DPP-4 inhibitor BI 1356 is dominated by saturable binding to its target in rats. Biopharm Drug Dispos 30: 229–240.
10. Salazar JJ, Ennis W, Koh TJ (2016) Diabetes medications: Impact on inflammation and wound healing. J Diabetes Complications 30: 746-752.
11. Mentlein R (1999) Dipeptidyl-peptidase IV (CD26)-role in the inactivation of regulatory peptides. Reg Pept 85: 9-24.
12. Boonacker E, Van Noorden CJ (2003) The multifunctional or moonlighting protein CD26/DPPIV. Eur J Cell Biol 82: 53-73.
13. Sato A, Ogita H (2017) Pathophysiological implications of dipeptidyl peptidases. Curr Protein Pept Sci18: 843-849.
14. Röhrborn D, Wronkowitz N, Eckel J (2015) DPP4 in diabetes. Front Immunol 6: 1-20.
15. Kieffer TJ, McIntosh CH, Pederson RA (1995) Degradation of glucose-dependent insulinotropic polypeptide and truncated glucagon-likepeptide 1 *in vitro* and *in vivo* by dipeptidyl peptidase IV. Endocrinology 136: 3585-3596.
16. Nguyen AD, Herzog H, Sainsbury A (2011) Neuropeptide Y and peptide YY:

Important regulators of energy metabolism. Curr Opin Endocrinol Diabetes Obes18: 56-60.

17. Suvas S (2017) Role of substance P neuropeptide in inflammation, wound healing and tissue homeostasis. J Immunol 199: 1543-1552.
18. Yu DM, Yao TW, Chowdhury S, Nadvi NA, Osborne B, et al. (2010) The dipeptidyl peptidase IV family in cancer and cell biology. FEBS J 277: 1126-1144.
19. Parvardia JK, Keswani SG, Vaikunth S, Mldonado AR, Marwan A, et al. (2007) Role of VEGR in small bowel adaptation after resection: the adaptive response is angiogenesis dependent. Am J Physiol Gastrointest Liver Physiol 293: 591-598.
20. Botusan IR, Sunkari VG, Savu O, Catrina AI, Grünler J, et al. (2008) Stabilization of HIF-1alpha is critical to improve wound healing in diabetic mice. Proc Natl Acad Sci U S A 105: 19426-19431.
21. Xiao-Yun X, Zhao-Hui M, Ke C, Hong-Hui H, Yan-Hong X (2011) Glucagon-like peptide-1 improves proliferation and differentiation of endothelial progenitor cells via upregulating VEGF generation. Med Sci Monit 17: BR35-41.
22. Bodnar RJ (2015) Chemokine regulation of angiogenesis during wound healing. Adv Wound Care (New Rochelle) 4: 641-650.
23. Zhang JM, An J. (2007) Cytokines, inflammation and pain. Int Anesthesiol Clin 45: 27-37.
24. Cahn A, Cernea S, Raz I (2016) An update on DPP-4 inhibitors in the management of type 2 diabetes. Expert Opin Emerg Drugs 21: 409-419.
25. Chen XW, He ZX, Zhou ZW, Yang T, Zhang X, et al. (2015) Clinical pharmacology of dipeptidyl peptidase 4 inhibitors indicated for the treatment of type 2 diabetes mellitus. Clin Exp Pharmacol Physiol 42: 999-1024.
26. Ahrén B (2008) Emerging dipeptidyl peptidase-4 inhibitors for the treatment of diabetes. Expert Opin Emerg Drugs 13: 593-607.
27. Röhrborn D, Wronkowitz N, Eckel J (2015) DPP4 in diabetes. Front Immunol 6: 386.
28. Samikannu B, Chen C, Lingwal N, Padmasekar M, Engel FB, et al. (2013) Dipeptidyl peptidase IV inhibition activates CREB an improves islet vascularization through VEGF-A/VEGFR-2 signaling pathway. PLoS One 8: e82639.
29. Schürmann C, Linke A, Engelmann-Pilger K, Steinmetz C, Mark M et al. (2012) The dipeptidyl peptidase-4 inhibitor linagliptin attenuates inflammation and accelerates epithelialization in wounds of diabetic ob/ob mice. J Pharmacol Exp Ther 342: 71-80.
30. Fadini GP, Boscaro E, Albiero M, Menegazzo L, Frison V, et al. (2010) The oral dipeptidyl peptidase-4 inhibitor sitagliptin increases circulating endothelial progenitor cells in patients with type 2 diabetes: Possible role of stromal-derived factor-1alpha. Diabetes Care 33: 1607-1609.
31. Wang PH, Huang BS, Horng HC, Yeh CC, Chen YJ (2017) Wound healing. J Chin Med Assoc 17: 30308-8.
32. Maddaluno L, Urwyler C, Werner S (2017) Fibroblast growth factors: key players in regeneration and tissue repair. Development 144: 4047-4060.
33. Yousuf Y, Amini-Nik S (2017) The role of myeloid lineage cells on skin healing and skin regeneration. J Tissue Sci Eng 8: 202.
34. Qing C (2017) The molecular biology in wound healing & non-healing wound. Chin J Traumatol 20:189-193.
35. Greenhalgh DG (2003) Wound healing and diabetes mellitus. Clin Plast Surg 30: 37-45.
36. Tsourdi E, Barthel A, Rietzsch H, Reichel A, Bornstein SR (2013) Current aspects in the pathophysiology and treatment of chronic wounds in diabetes mellitus. Biomed Res Int 2013: 385641.
37. Falanga V (2005) Wound healing and its impairment in the diabetic foot. Lancet 366: 1736-1743.
38. Waumans Y, Baerts L, Kehoe K, Lambeir AM, De Meester I (2015) The dipeptidyl peptidase family, prolyl oligopeptidase and prolyl carboxypeptidase in the immune system and inflammatory disease, including atherosclerosis. Front Immunol 6: 387.
39. Itou M, Kawaguchi T, Taniguchi E, Sata M (2013) Dipeptidyl peptidase-4: A key player in chronic liver disease. World J Gastroenterol 19: 2298-2306.
40. Abe K, Tilan JU, Zukowska Z (2007) NPY and NPY receptors in vascular remodeling. Curr Top Med Chem 7: 1704-1709.
41. Metzemaekers M, Van Damme J, Mortier A, Proost P (2016) Regulation of chemokine activity – A focus on the role of dipeptidyl peptidase IV/CD26. Front Immunol 7: 483.
42. Goren I, Kampfer H, Podda M, Pfeilschifter J, Frank S (2003) Leptin and wound inflammation in diabetic ob/ob mice: Differential regulation of neutrophil and macrophage influx and a potential role for the scab as a sink for inflammatory cells and mediators. Diabetes 52: 2821–2832.
43. Baticic Pucar L, Pernjak Pugel E, Detel D, Varljen J (2017) Involvement of DPP IV/CD26 in cutaneous wound healing process in mice. Wound Rep Reg 25: 25-40.